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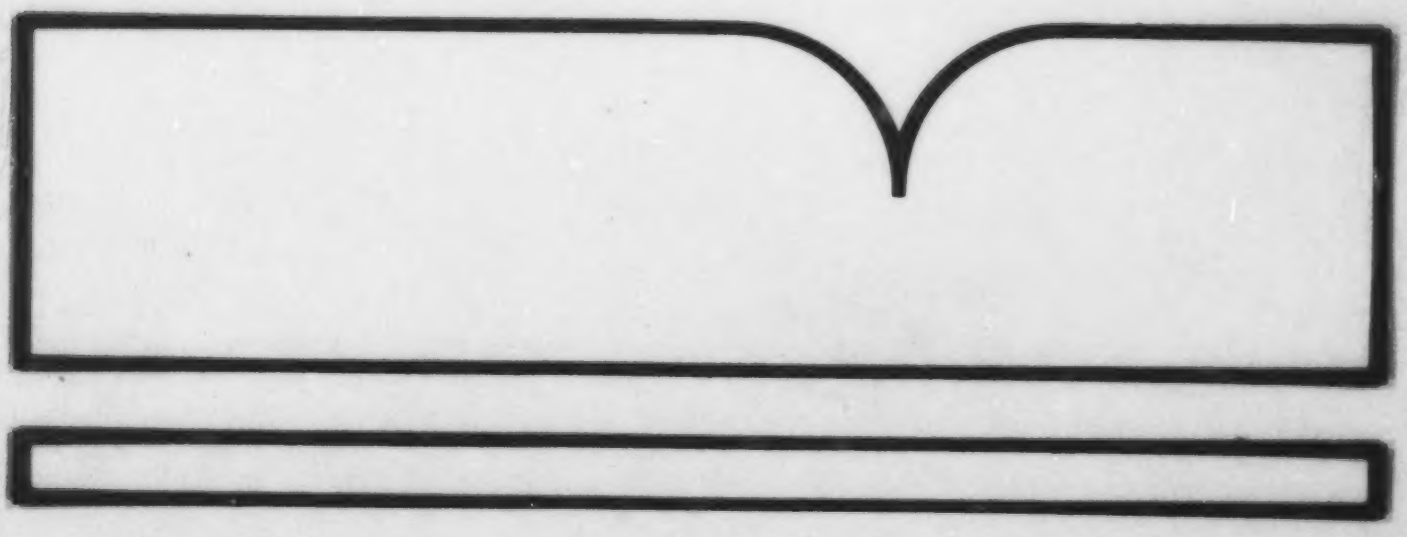

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16. ABSTRACT

This represents the first in a series of lectures sponsored by the Agency to present a range of perspectives on controversial environmental and health issues from the vantage points of distinguished scientists. The views expressed are, therefore, not necessarily the views of the U.S. EPA. The lecture discusses what is known about the health and carcinogenic effects associated with low doses of ionizing radiation. It points out the scientific consensus that there are no reproducible studies unequivocally demonstrating the effects of low-level ionizing radiation and distinguishes between scientific fact and public policy.

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Distinguished Lecturer Series

Rosalyn S. Yalow: Biologic Effects of Low-Level Ionizing Radiation

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The following is the first of a planned series of lectures to be sponsored by the Office of Research and Development, U.S. Environmental Protection Agency. The views expressed in this lecture are the speaker's own, not to be construed as the Agency's. This material has not been subject to the normal Agency peer and administrative review procedures and, therefore, does not necessarily reflect the Agency's position on any aspect of the issue discussed.

As the scientific arm of the Agency, the Office of Research and Development has the responsibility to advance the state of scientific knowledge about the environment. Highlighting emerging issues and providing scientific perspectives on current problems is an important part of our responsibility. We intend that our lecture series will present a range of perspectives on various aspects of health and environmental research, from the vantage points of well-known and distinguished scientists. The points of view represented in our lectures will be varied, perhaps conflicting, and not necessarily in agreement with Agency policy. But scientific progress depends upon the free exchange of diverse opinions.

Biologic Effects of Low-Level Ionizing Radiation*

By Rosalyn S. Yalow

ROSALYN S. YALOW, of the Veterans Administration Medical Center and Montifore Hospital in the Bronx, is a distinguished researcher in the field of medical physics. She won the Nobel Prize in 1977 for her work in radioimmunoassay development. Her recent publications include "Radioactivity in the Service of Man;" "Disposal of Low-Level Radioactive Biomedical Wastes: A Problem in Regulation, Not Science;" and "Reappraisal of Potential Risks Associated with Low-Level Radiation."

We live in a world in which the perception of reality is too often confused with reality and there are few fields in which more confusion exists than in the popular perception of the hazards of exposure to low level radiation and low level radioactive wastes. Much of the fear of radiation has been generated by the association of radiation and radioactivity with nuclear explosions and nuclear war. So phobic is the fear that the new medical imaging modality "nuclear magnetic resonance" or NMR has been renamed Magnetic Resonance or MR to avoid the bad word "nuclear." What I would like to discuss today is not philosophy but science—what do we know about health effects, and in particular, the carcinogenic effects associated with low doses of lightly ionizing radiation. Since there are tens of thousands of papers in this field, I have obviously had to be selective in choosing studies to discuss.

Before discussing radiation effects, let me define some units. A rad is a unit of absorbed dose or energy absorbed per unit mass from ionizing radiation and corresponds to 100 ergs/gram. Densely ionizing radiation such as that associated with α particles, protons or fast neutrons is more effective in producing deleterious biologic effects than is the lightly ionizing radiation associated with β, γ- or X-radiation. A rem is a unit that takes into account the relative biologic effectiveness (RBE) of lightly (low linear energy transfer, LET) and densely (high LET) ionizing radiation. A rem is an absorbed dose that produces the same biologic effect as 1 rad of low LET radiation. Rad and rem can be used interchangeably for low LET radiation. The RBE is not a constant for any ionizing particle but depends to some extent both on its energy and the biologic effect under observation.

The question to be addressed "How low is low" or are there levels of radiation below which one cannot discern deleterious effects. Much of what is known about the biologic effects of ionizing radiation has been obtained from epidemiologic studies of humans exposed to high doses and/or at high dose rates. Over about the past three decades national and international standard-setting bodies concerned with establishing radiation protection guidelines have accepted the hypothesis of a linear dose-effect extrapolation with no threshold, on the assumption that this provided a generous safety factor for predicting possible radiation-induced deleterious effects. According to this hypothesis, there would be the same number of radiation-related cancers or other biologic effects, among a 100 thousand people each receiving 100 rem as among 100 million people each receiving 100

*Presented at the Environmental Protection Agency, Washington, DC, on August 17, 1984.

mrem. Can this hypothesis be tested? To put this concept into the proper perspective let us consider that there were about 80000 survivors of the Hiroshima-Nagasaki bombings. The survivors received doses less than 400 rems. To deal in round numbers one can treat this group as 100 thousand people receiving about 100 rem. In almost three decades the excess radiation-related deaths in this group were less than 200. Natural background radiation in most of the United States is 100 mrem/year, due to cosmic rays, natural radioactivity of the soil and building materials and the self-contained radioactivity in all living things, each contributing about one-third. If the linear extrapolation hypothesis were valid, based on the Japanese experience, one would expect about 200 deaths due to background radiation. Since among 100 million Americans there are about 200 thousand cancer deaths per year, natural variations in this death rate would not permit ascertainment of the few hundred deaths that might be attributable to background radiation. This rough calculation points out the absurdity of Public Law 97-414 that requires "the Secretary of Health and Human Services to devise and publish radioepidemiologic tables . . . These tables shall show a probability of developing each radiation cancer associated with receipt of doses ranging from 1 mrad to 1000 rads . . . ." It must be appreciated that 1 mrad is about 1% of natural yearly background and that a round trip flight from Washington to Los Angeles increases radiation exposure by 5 mrad. Most of us would accept that the probability of causation of cancer at dosages in the mrad range is obviously zero to many significant figures. As a member of the committee attempting to construct these tables, I can assure you that the uncertainties even at doses of many rads are subject to such controversy that one should not "require" attention to exposure in the mrad range. However, such legislation creates a mind-set in the public that radiation at the mrad level is a cause for concern.

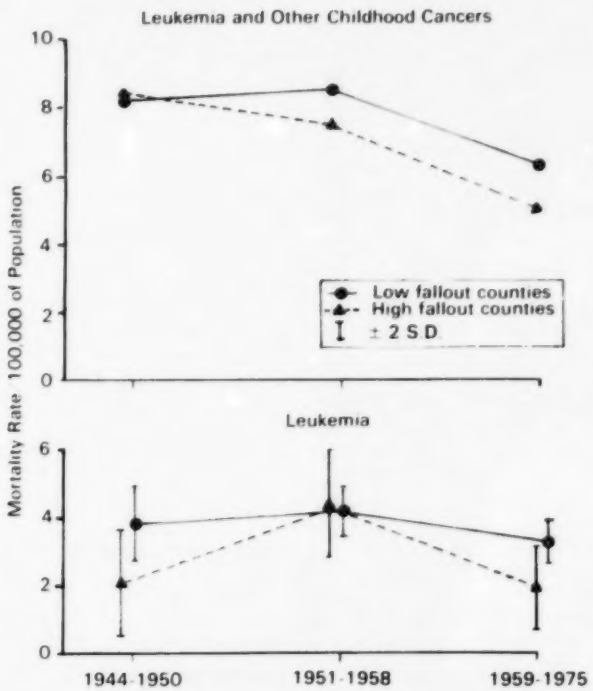
There have been a number of studies attempting to detect deleterious health effects in regions of the world where natural background radiation is increased. One such study was performed in China by examining 150,000 Han peasants with essentially the same genetic background and same life style. Half of them lived in a region where they received an almost three-fold higher radiation exposure because of radioactive soil (1). More than 90% of the progenitors of the more highly exposed group had lived in the same region for more than 6 generations. The investigation included determination of radiation level by direct dosimetry and evaluation of a number of possible radiation-related health effects including chromosomal aberrations of peripheral lymphocytes, frequencies of hereditary diseases and deformities, frequency of malignancies, growth and development of children and status of spontaneous abortions. This study failed to find any discernible difference between the inhabitants of the two areas. The authors of this study concluded that either there may be a practical threshold for radiation effects or that any effect is so small that the cumulative radiation exposure to three times the usual natural background resulted in no measureable harm after six or more successive generations.

There are regions in the United States where natural background radiation is also increased. In the Rocky Mountain States the average radiation exposure is about twice that on the East and West coasts because of increased cosmic rays at their higher elevations and natural radioactivity of the soil. However, death rates due to cancer in these states are among the lowest in the country. It is possible that an appropriate statistical analysis would reveal that the racial, ethnic, age distribution or other factors might account for the lower cancer death rates in these states. However, when Mason and Miller (2) compared the age-adjusted risk ratio for mortality from malignancies for Caucasians in Denver and Salt Lake City with those in San Francisco and Seattle-King County, Washington, they observed that the leukemia incidence was slightly but not significantly lower and the incidence of other cancers was significantly lower in the higher radiation exposure cities. An inverse relationship between elevation (hence higher radiation exposure) and mortality from leukemias and lymphomas has also been reported (3). Others have concluded (4) that in the United States there is no relation between increased background radiation and leukemia. There are regions of the world in India and in Brazil where natural background radiation is up to 10-fold higher than usual (~1 rem/year) and deleterious health effects have been looked for and not found (5-9). This is not surprising since even were the linear extrapolation hypothesis valid, the populations involved are too small to detect increased malignancies above the natural variation in the incidence of the diseases. However, these studies emphasize the difficulties in assessing probablity of causation at low doses and dose rates.

Senator Hatch was undoubtedly stimulated to sponsor Public Law 97-414 mandating the radioepidemiological tables in response to several widely publicized reports asserting that the cancer risks from low radiation exposures are much higher than those estimated according to the linear extrapolation hypothesis. One report that was of particular concern to his constituents was that of Lyon et al. (10) who reported that leukemia mortality in children was increased in those

counties in Utah receiving high levels of fall-out from the atmospheric nuclear testing conducted in 1951-1958 compared to the mortality in low fall-out counties and in the rest of the United States. Let us examine the original data. In Figure 1 are shown the mortality rates for leukemia and for all cancers, including leukemia, for children in high and low fall-out counties in Utah. The 1944-1950 period represents the pre-fallout control low-exposure cohort. The 1951-1958 group was considered to be the high-exposure cohort, that is, those born during the period of maximum above-ground nuclear bomb testing in Nevada. The second low-exposure cohort was the group born after most, but not all, of the above-ground testing had ended. From a perusal of Lyon's data it could reasonably be concluded that on the average during the entire 30-year period the high fall-out counties might have had a lower incidence of leukemia than the low fall-out counties, but that the uncertainties in the determinations are so large that one cannot reliably conclude whether or not there is a trend. If one considers the sum of childhood malignancies (leukemia plus other cancer deaths) there appears to be a generally downward trend, with the drop in the high-fallout counties being somewhat greater than in the low-fallout counties, although if the standard deviations had been included the differences would not have been significant. The news headlines following interviews with Dr. Lyon would have been less sensational if he had stated that his data had shown no relation between the totality of childhood malignancies and the atomic tests of the 1950's rather than selectively reporting what would appear to me, as an experimental scientist whose results do not depend on marginal p-values, to be an inconclusive study of the relation between leukemia and fall-out. Lyon's paper in the New England Journal of Medicine was criticized in the same and later issues of the Journal by several biostatisticians (11-13). In general, their criticisms were related to the apparent under-reporting or misdiagnosis in the earlier cohort and to errors in small sample analysis. For instance, Bader (12) presented a year-by-year listing of leukemia cases in Seattle-King County, which has a larger population than the Southern Utah counties, and noted that there were only two cases in 1959 and 20 in 1963 among the 217 cases reported from 1950 to 1972. Thus, a ten-fold difference in annual incidence rates when the number of cases is small simply represents statistical variation. Although the yearly distribution of leukemia cases had not been reported in any of Lyon's papers or in the associated publicity, it was however tabulated in the Government Accounting Office Report on the Problems in Assessing the Cancer Risks of Low-Level Ionizing Radiation Exposure (14). Table 1 is taken from that report. It is to be noted that the so-

Figure 1. **Data reproduced in graphical form from (10). Total childhood malignancies including leukemia (top) and childhood leukemia in high fall-out and low fall-out regions of Utah according to study of Lyon et al.**



called excess leukemia cases reported by Lyon et al. (10) was due to a clustering of 13 cases in 1959 and 1960. In fact, 22 of the 32 leukemia cases occurred in 1951-1960, i.e., during the first 10 years of testing. Since there is a several year latency period between radiation exposure and induction of leukemia, were the excess leukemia deaths a consequence of nuclear testing in the 1950's; they would have been more likely to occur after 1960 rather than before.

Furthermore, a new estimate of external radiation exposure of the Utah population based on residual levels of ^{137}Cs in the soils has shown that the mean individual exposure in what Lyon deemed to be the "high fall-out counties" was 0.86±0.14 rad compared to 1.3±0.3 rad in the "low fall-out counties" (15). Even in Washington County, the region in which the fall-out arrived the earliest (less than 5 hours after the test) the estimated exposure to its 10,000 population averaged only 3.5±0.7 rads—quite comparable to natural background radiation in that region over a 20-30 year period. Thus on the basis of the Japanese experience the exposure from fall-out was too low to expect an

Table 1. Year of Bomb Testing in Nevada[a] and Year of Death from Leukemia for the Southern Utah High-Exposure Cohort[b]

	Test Yield (kilotons)	Number of Deaths Southern Utah High-Exposure Cohort
51	112	0
52	104	3
53	252	2
54	—	0
55	167	2
56	?	2
57	343	0
58	38	0
59	—	7
60	—	6
61	—	2
62	101	1
63	<20	1
64	<20	0
65	<80	1
66	<60	1
67	20-200	2
68	<60	1
69	20-200	1

[a]Data taken from reference 10
[b]From data supplied by Dr. Lyon for the report in reference 14, pages XVIII-43

increase in leukemia and a careful perusal of the raw data would suggest that none was found.

Another report that has received publicity far beyond its scientific merit is the Mancuso study of workers at the Hanford Laboratories, the site of several of the then AEC's reactors. The history of this study dates back to 1964 when Dr. Mancuso was awarded a contract to investigate for the AEC the health of these workers. Dr. Barkev Sanders, a statistician, and Dr. Allen Brodsky, a health physicist, were co-investigators in this project. Annual project reports for many years suggested only that there were negative findings regarding a link between cancer and radiation and Drs. Sanders and Brodsky left the project. There were no papers published during the period in which they were involved in the analysis of the data. In about 1976, Mancuso was joined by the pediatrician Stewart and the statistician Kneale who had acquired a reputation for their studies on relationships between diagnostic X-rays and childhood cancers. Together they wrote a controversial paper purporting to show that workers at Hanford had a statistically significant increase in the incidence of two types of cancer, multiple myeloma and cancer of the pancreas (16). According to Table 10 of their paper the mean cumulative radiation dose for Hanford workers who subsequently died from cardiovascular disease was 1.05 rads; for solid tumors 1.3 rads; for leukemias and lymphomas 2.2 rads. This excess radiation exposure is quite comparable to the excess received by living in Colorado for 10 to 20 years—and Colorado has a low cancer death rate. The evidence in the Mancuso report that has not been widely publicized was that Hanford workers receiving the highest radiation doses (greater than 15 rem) had a lower death rate from all causes and from all malignant neoplasms than expected in a control population. However, because of the small numbers of workers who received this exposure and the small number of cancer deaths in this group, (a total of 14 cancer deaths compared to 24 expected) the distribution among the different malignancies appeared to have a pattern not identical with that found in much larger groups. Subsequently, both Dr. Brodsky and Dr. Sanders, who initially collaborated with Dr. Mancuso, have been highly critical of the Mancuso paper. An independent analysis by Gilbert and Marks is most revealing (17). The positive correlation purported to be demonstrated in the Mancuso report appears to be due to 3 deaths from pancreatic cancer in workers receiving more than 15 rem cumulative exposure. However, according to Gilbert and Marks (17) this diagnosis had been confirmed only in 1 case. Furthermore, it should also be noted that the Atomic Bomb Casualty Committee report described a much larger cohort with much higher radiation exposures (up to 400 rads) and found no positive link between pancreatic neoplasms and radiation (18). The second category of excess cancer deaths was reported to be multiple myeloma, which included 3 cases compared to an expected number of 0.6 (16). Whether this excess of 2 deaths in this category represents a statistical variation or the effect of another carcinogen cannot be determined. Nonetheless, since among those receiving a cumulative exposure of 15 rems, the observed number of subjects with malignancies was only 14 compared to an expected 24 in a control population, one could be tempted to conclude that radiation at this level is protective against malignancies.

To demonstrate how legislation is sponsored in response to special interest groups rather than rational analysis, let me pose the following problem. Let us assume that there are two groups who received exposure to radiation. Group A consists of 6500 people who were not badged but who received radiation exposures probably in the range of 10-50 rems, or perhaps more; Group B consisted of 39 who received more than 25 rem, 1400 who received between 5 and 25 rem and another 5000 who received between 3 and 5 rem. Which of the two groups should have been favored with respect to compensatory legislation concerning possible radiation-related health effects? The logical answer would be the Group A who received the larger

radiation exposure. Now let me identify for you Groups A and B, the legislative act and the known health effects. Group A was a group who were trained during World War II as radiology technicians and who subsequently served in that role for a median period of 24 months. Description of their training (19) included the statement that "During the remaining two hours of this period the students occupy themselves by taking radiographs of each other in the positions taught them that day." It was noted (19) that the students did not receive a skin erythema dose nor did they show a drop in white count—monitoring procedures that are insensitive to acute doses less than 100 rem. The cumulative exposures of these radiology technicians were not monitored. However, the radiation exposure of technologists at a more modern installation, Cleveland Clinic, was monitored in 1953 and found to be in range of 5-15 rad/year (20). Army technologists a decade earlier probably received greater exposures. Hence my estimate of 10-50 rem during their period of service. Yet, a followup of these 6500 radiology technicians (21, 22) for a period of 29 years revealed no increase in malignancies when compared with a control group of similar size consisting of Army medical, laboratory or pharmacy technicians.

Who was Group B? This group consists of those who entered Hiroshima and Nagasaki after the bombing and who received less than 0.1 rem during the occupation and the 220,000 Department of Defense (DOD) personnel involved in the atmospheric nuclear testing in the Pacific Ocean and Nevada. Among this large group only 1400 received more than 5 rem (23). Among these 1400 were 39 who received over 25 rem as a result of a wind shift during the 1954 Bikini testing. A follow-up of these 39 men almost 30 years later revealed that 4 were dead from causes not associated with radiation (trauma, heart attacks). Of the 35 who were notified, only 18 desired medical examinations, 7 refused and 10 failed to reply. No adverse health effects associated with radiation were found in those examined.

Further to put in proper perspective the cumulative radiation exposure among Armed Services personnel associated with nuclear testing, it should be appreciated that in the early years of the draft those accepted into the Armed Forces, and many of those rejected on medical grounds, a group numbering over 12 million persons, received chest photoroentgenograms. Unlike ordinary X-ray examinations of the chest, these deliver 1 to 5 rad skin dose (24). In addition, some of the Armed Services received considerable X-ray exposure secondary to service-related injuries and of course there were the higly exposed radiology technicians. None of these are included in Public Law 97-72 (25) which provides that "a veteran who the (Veterans Administration) Administrator finds was exposed while serving on active duty to ionizing radiation from the detonation of a nuclear device in connection with such veteran's participation in the test of such a device or with the American occupation of Hiroshima and Nagasaki, Japan, during the period beginning on September 11, 1945, and ending on July 1, 1946, may be furnished hospital care or nursing home care for any disability notwithstanding that there is insufficient medical evidence to conclude that such disability may be associated with such exposure."

There is no logic in giving special privileges to some veterans who received radiation exposure and not to all receiving equivalent exposure. Perhaps this legislation was in response to another highly publicized report concerning 9 cases of leukemia among 3200 men who participated in a nuclear test explosion in 1957 (26). The radiation exposures of 8 of the 9 men were monitored; 3 received between 1 and 3 rem; 3 received less than 0.1 rem. Since the 20,000 people exposed in Hiroshima-Nagasaki to doses between 1 and 9 rads showed no increase in malignancies, including leukemia, the study by Caldwell et al. (26) concerning only 3200 people exposed in this dose range is obviously flawed; the most probable reason is once again the error inherent in small number statistics. By the time of diagnosis all the leukemia cases had received more radiation from natural background than from Operation Smoky.

Can epidemiologic studies permit testing of the validity of the linear extrapolation hypothesis in estimating effects at low doses and dose rates? The answer is unequivocally no. As Land has pointed out (27) to test this hypothesis, for instance in radiation-induced breast cancer, a sample size of 100 million women would be required to be certain of an increased radiologic incidence following an acute exposure of 1 rem to both breasts at age 35. Such a sample is hardly practical. Therefore, a case-control approach, in which the sample consists of a fixed number of cancer cases and a fixed number of matched non-cases or controls, is used. Land has calculated (27) that using this cohort approach only 1,000,000 women would be required to be certain of a radiation effect from 1 rem. Of course, in the case-control approach to evaluation of radiation and other carcinogens, a sufficient number of subjects are never included and there is not random selection of cases and controls. Hence, the data presented simply do not have statistical significance and subtle sources of bias could well account for purported observed effects. For instance, MacMahon has reported (28) that children born after their mothers had received one to six pelvic radiographs (average dose per radiograph was 1 rad) were 42% more likely to die

of cancer in the first 10 years of life then were children not irradiated *in utero*. Using the same case-control method of analysis MacMahon et al. (29) also reported that drinking 1 to 2 cups of coffee a day introduced a relative risk of 2.6 in developing cancer of the pancreas and further suggested that coffee drinking at this level can account for more than 50% of the cases of pancreatic cancer. However, since coffee drinking is familiar and radiation is not, most people would discount that his case-control analysis proves that such modest coffee drinking is a risk factor for pancreatic cancer, particularly since the effect did not appear to be dose-related in men—the risk factor was the same, 2.6, whether consumption was 1-2 cups or greater than 5 cups a day. There are other reasons for reluctance in accepting his analysis. For instance, the risk factor was twice as great for ex-smokers compared to current smokers drinking 1 to 2 cups of coffee per day, a rather unlikely finding since it is commonly accepted that smoking is a carcinogen or promoter of other carcinogens. The MacMahon et al. (29) report on the association between coffee drinking and cancer of the pancreas is, however, in a sense less-flawed than his earlier report (28) on the association between prenatal radiation and early cancer death. In the latter study there was clearly a bias in that no account was taken of the fact that the exposed mothers had medical conditions that prompted the diagnostic X-rays.

Webster has provided a simple demonstration of the problem of small number observations by determining the counting rate from a weakly radioactive source (30). Such a counting rate, like cancer events, follows Poisson statistics. In 20 successive periods the counting rate varied from 0 to 8 counts per unit time, with an average of 4. As shown in Table 2 the actual occurrence of a particular counting rate to the probability of its occurrence ranges from 0.6 to 2.8—these ratios are equivalent to the "relative risk" ratio using the case-control approach in epidemiologic studies—except that there was no bias introduced in the "control" or Poisson probability distribution.

For almost 30 years committees concerned with radiologic protection accepted the linear extrapolation hypothesis without correction for dose rate on the basis that it overestimated potential radiation-related risks. This has left the impression that it is an established fact that any level of radiation, no matter how small, carries some risk even if that risk is not measurable. In the latest report of the National Academy of Sciences Committee on the Biologic Effects of Ionizing Radiation (BEIR III Report) (31), it was concluded that a linear-quadratic extrapolation was to be preferred although it was also stated that the scientific basis for making estimates of the

Table 2. Poisson Statistics: The Problem of Small Number Observations*

	No Observed	Probability (%)	Occurrence Probability
Actual counts observed during 20 consecutive counting periods	6,3,5,4,2,2,4,4, 7,3,8,6,6,2,0,5,		2,3,6,1
Theoretical expectations with Poisson distribution	0	1 8	2 8
	1	7 3	0 63
	2	14 6	1 37
	3	19 5	0 77
	4	19 5	0 77
	5	15 6	0 64
	6	10 4	1 90
	7	5 9	0 85
	8	3 0	1 60

*Taken from Reference 30.

carcinogenic risk of low-dose low-LET whole body radiation is inadequate. The data are simply not available that would permit determination as to whether there is any risk associated with radiation at doses below 10 rads.

There is one large group of subjects with total body exposures in this dose range, i.e., patients treated with radioactive iodine, ^{131}I for hyperthyroidism. As of 1968 it was estimated that 200,000 people were so treated and the number has probably since doubled. A study of 36000 hyperthyroid patients from 26 medical centers of whom 22000 were treated with a single dose of ^{131}I and most of the rest with surgery revealed no difference in the incidence of leukemia between the two groups (32). The average bone-marrow dose was about 8 to 10 rads, about half of which was delivered within one week. The follow-up for the ^{131}I-treated group averaged 7 years, quite long enough to have reached the peak incidence, as determined from the Hiroshima-Nagasaki experience. A subsequent follow-up three years later again revealed no differences in the leukemia rate between the two groups (33). This study emphasizes the importance of having an appropriate control group. Earlier studies had suggested that the occurrence of leukemia in hyperthyroid patients following ^{131}I therapy was 50% greater than that of the natural population (34, 35). However, it appears from this study that there is an increased incidence of leukemia in hyperthyroidism, irrespective of the type of treatment (32).

The question may be addressed as to whether a large epidemiologic study could or should be undertaken to follow-up the several hundred thousand who have been treated with ^{131}I for hyperthyroidism. I believe the feasibility of such a study should be examined. It has the potential for

answering the question as to whether general body exposure in the 10 rad range delivered at a relatively low dose rate is carcinogenic. However, since it appears that hyperthyroidism *per se* may be associated with leukemia, the appropriate control group should be, as in the study of Saenger et al. (32), patients treated with surgery. I doubt if it is currently possible to obtain an age-matched surgically treated group since ^{131}I has certainly become the treatment of choice for definitive therapy. In evaluating whether hyperthyroid patients treated with anti-thyroid drugs until remission would be suitable as a control group, the potential of these drugs for inducing leukemia must also be considered.

There have been several other negative studies in which induction of leukemia as a consequence of radiation was sought for and not found. The BEIR III Report did not consider early papers (36, 37) that observed no increase in leukemia in women treated for cervical cancer with either intercavitary radium, external radiation or both. Perhaps the reasons for neglecting consideration of these papers was the incomplete patient follow-up in these earlier studies. However, a recent report (38) of an international collaborative study of 31,219 women with cervical cancer, of whom 28,490 received radiation therapy and 2729 did not, revealed that in the irradiated group 15.5 cases of leukemia were expected and 13 were observed (relative risk=0.8) (95% confidence levels 0.4-1.4) and in the non-irradiated group 2 cases of leukemia were observed as compared with the 1.0 expected. The follow-up was long enough to have included the 4 to 8 year period of leukemia peaking observed with the Japanese atom bomb survivors. The consistency of these studies (36-38) would suggest that there is no detectable leukemogenic effect in patients with cervical cancer following radiotherapy. The cohort size of this study is quite comparable to the Court-Brown and Doll study showing increased incidence of leukemia in patients irradiated for ankylosing spondylitis (39, 40). It does remain a mystery as to why radiotherapy would appear to be leukemogenic in one disease and not in another when the therapeutic doses are in the same range although not delivered to the same body region.

It is commonly accepted that early radiation workers had an increased incidence of malignancies. For the most part, their radiation exposures cannot be estimated. The classical picture of the Curies working in their shed for 4 years while separating and purifying radium and polonium is one which will never be repeated. It is not surprising that Marie Curie died from aplastic anemia, probably secondary to the radiation exposure she received in her laboratory and during her experiences in World War I when she personally provided X-ray services just behind the front lines, trained X-ray technicians and installed 200 radiologic rooms. What is surprising is that she did not die until 1934 at the age of 66 in spite of cumulative exposures that must have been thousands of rems. What about more recent radiation workers with lesser exposures? A recent report of the mortality from cancer and other causes among 1338 British radiologists who joined radiologic societies between 1897 and 1954 revealed that in those who entered the profession before 1921 the cancer death rate was 75% higher than that of other physicians but that those entering the profession after 1921 had cancer death rates comparable to other professionals (41). Although the exposure of the radiologists was not monitored, it is estimated that those who entered between 1920 and 1945 could have received an accumulated whole-body dose of the order of 100 to 500 rad.

It seems obvious from these sampling of reports that human studies in the low dose, low-dose rate range are complicated by the biases introduced by the case-control methodology, the limitations of small number statistics and the natural variation in disease patterns in a heterogeneous human population. Because of these inherent limitations, it seems unlikely that human studies will ever answer definitively the question as to whether there is a threshold for radiation-induced carcinogenesis.

Animal studies have certain advantages: the animals are inbred and are not subject to the genetic and environmental variability of a human population; at present it is possible to expose animals but not humans to graded radiation doses at different dose rates. The inherent limitation of such studies is that it would be enormously expensive to maintain the large groups of animals that would be required to evaluate effects at truly low doses and dose rates. The conclusion of many studies of different tumors in different animals is that for a given total dose there was generally decreased tumorigenesis when the radiation was delivered at a lower dose rate, but that the reduction factor was dependent on the tumor and the species of animals (42). None of these studies have been performed at truly low dose rates. The studies by Ulrich and Storer (43) on tumorigenesis in RFM mice revealed that the ^{137}Cs gamma-ray irradiation is delivered at 8.3 rad/day, i.e., 25,000 times natural background, there is a threshold of about 50 rads before an increased incidence of ovarian tumors or thymic lymphomas is observed. The threshold appeared to be no more than a few rads when the irradiation dose rate was 45 rad/min. Studies at even lower dose rates, for instance at about 100 times natural background, would require an enormous number of animals and are really not practical.

Without developing a detailed theoretical model for radiation carcinogenesis, it can be expected that, since human beings are more than 75% water, low-LET ionizing radiation is probably largely absorbed in the water with production of free radicals. Thus many of the biochemical changes initiated in the cell and, in particular, damage to cellular DNA, are probably a consequence of the indirect action of the products of water radiolysis. If molecules which scavenge radicals and which are normally present in tissue exceed the concentration of free radicals generated at low dose rates, there may well be no initiating event, i.e., damage to DNA. The threshold could be the dose rate at which the free radicals overwhelm the scavengers—and this may be dependent on species of animals and specific tissue. This is a tenable hypothesis but one that is not readily verifiable.

In addition to concerns with carcinogenesis, there is considerable fear of the risks of genetic effects from radiation. This was considered extensively in the BEIR III report (31) and it was concluded that since radiation-induced transmitted genetic effects have not been demonstrated in man, estimates of genetic risks must be based on laboratory data obtained at high dose rates. Schull et al. (44) have concluded on the basis of studies of the children born to survivors of the Hiroshima-Nagasaki bombings, that the estimated doubling dose for genetic changes would be about 150 rem, a value some four-fold higher than the results from experimental studies on mice. Furthermore, this represents simply an estimate since they reported that in *no* instance was there a statistically significant effect of parental exposure. It should be noted also that many investigators have found that chronic irradiation in mice is about three-fold less effective than acute irradiation. This would effectively raise the doubling dose for prolonged exposure in man to about 500 rem. Furthermore, since none of the studies in mice were performed at truly low dose rates, one cannot really determine what the doubling rate would be for background radiation.

In my introduction to this presentation I raised the question "How low is low?" or are there levels of radiation below which one cannot discern deleterious effects of radiation. The answer to that question is YES. The GAO report concludes (14) that "there is as yet no way to determine precisely the cancer risks of low-level ionizing radiation exposure, and it is unlikely that this question will be resolved soon." *Stating that there are levels below* which one cannot discern harmful effects of radiation is not the same as reaching conclusions concerning the existence of a threshold below which radiation effects in man does not occur. In science we can only accept as valid those laws that are subject to experimental proof. We can hypothesize, but we should not confuse hypothesis with reality. There is a problem in determining what kinds of studies should be funded in radiologic research. It is evident that epidemiologic studies cannot produce meaningful data about the existence of a threshold for radiation effects. Molecular and cellular studies may or may not give some insight about molecular or cellular effects but cannot answer important questions about repair mechanisms in the intact animal or man when radiation is delivered at low dose-rates. At present there are no really good ideas that would permit a breakthrough in the field of low-level radiation effects. Therefore, good scientists with imagination and insight are unlikely to work in a field in which the studies, at best, are pedantic and, at worst, are inevitably flawed. Thus, this field of research which is now primarily generated not by scientific interest but by Federal concern and Congressional mandate is not likely to attract investigators seeking to open new frontiers in science. It is essential to communicate to the public and through them to our government that each of us loses when scientific talent and funding is diverted from scientifically important and socially desirable investigations to predictably negative experimentation because of irrational fears generated by well-intentioned or ill-intentioned but often uninformed Cassandras.

Let me turn now, for a moment, from science to philosophy. Science, unlike religion, is not influenced by belief or divine revelation. In science we observe, hypothesize and reobserve in an attempt to determine whether the hypothesis is consistent with the observations. Scientists are not Aristotelians—if we want to determine the number of teeth in a horse's mouth we open its mouth and count the teeth. Sometimes the critical experiments cannot be performed with available tools. Thus, Newton's Laws, which were dogma for over two centuries, could not predict behavior at high velocities or atomic or subatomic dimensions. But this is simple compared to predicting the laws governing the much more complex interrelations in biologic systems including man. With respect to effects of low-level radiation, there is a consensus that there are no reproducible studies demonstrating unequivocally that such effects are demonstrable. The disagreement concerns how to extrapolate from higher dose rates and total doses to the non-measurable range. The BEIR III Report (31) concluded that a linear-quadratic extrapolation is the one most consistent with available data; Radford dissented and contended that the linear extrapolation hypothesis was appropriately conservative; Rossi claimed that a quadratic extrapolation should be employed. There are those who hold that there is no evidence which would exclude the possibility that there is a threshold below which there are no radiation effects. After all,

with what we have learned in recent years through studies in molecular biology there is every reason to believe we have repair mechanisms hitherto undreamed of. The disagreement in the low-level radiation field is about hypothesis—not observable facts. One could not determine the validity of Newton's Laws at sub-atomic dimensions until the tools became available. However, in that case there was no need to make policy decisions based on extrapolation. In the case of low-level radiation effects, public policy decisions need to be made in the absence of scientific evidence. It should be appreciated that these are arbitrary decisions based on philosophy not fact and may well change because of political or other considerations.

In conclusion let me quote from the National Council (NCRP) Report No. 43 on Radiation Protection Philosophy. "The indications of a significant dose rate influence on radiation effects would make completely inappropriate the current practice of summing of doses at all levels of dose and dose rate in the form of total person-rem for purposes of calculating risks to the population on the basis of extrapolation of risk estimates derived from data at high doses and dose rates. . . . The NCRP wishes to caution governmental policy-making agencies of the unreasonableness of interpreting or assuming "upper limit" estimates of carcinogenic risks at low radiation levels, derived by linear extrapolation from data obtained at high doses and dose rates, as actual risks, and of basing unduly restrictive policies on such an interpretation or assumption. Undue concern, as well as carelessness with regard to radiation hazards, is considered detrimental to the public interest." Would that all legislators and regulators would pay heed to these words!

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